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PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* YAAKOV NAPARSTEK,  
Appellant<sup>1</sup>

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Appeal 2010-010699  
Application 09/826,069  
Technology Center 1600

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Before CAROL A. SPIEGEL, TONI R. SCHEINER, and ERIC GRIMES,  
*Administrative Patent Judges.*

SPIEGEL, *Administrative Patent Judge.*

DECISION ON APPEAL<sup>2</sup>

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<sup>1</sup> The real party in interest is HADASIT MEDICAL RESEARCH SERVICES AND DEVELOPMENT COMPANY LTD. (Appellant's Brief under 37 C.F.R. § 41.37, filed 15 October 2009 and amended 3 February 2010 ("Br."), at 3). This decision also cites to the Examiner's Answer mailed 27 April 2010 ("Ans.") and the Specification ("Spec.") of Application 09/826,069 ("the 069 Application").

<sup>2</sup> The two-month period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

Appellant appeals under 35 U.S.C. § 134(a) from an Examiner's final rejection of all pending claims, claims 8-13 (Br. 5; Ans. 2). We have jurisdiction under 35 U.S.C. § 134. We AFFIRM.

I. Statement of the Case

The subject matter on appeal is directed to a method of treating systemic lupus erythematosus ("SLE") by using immunoadsorption plasmapheresis to selectively remove pathogenic SLE autoantibodies from an SLE patient. Claim 9 is illustrative and reads (Br. 27):

9. A method of treating a subject having systemic lupus erythematosus comprising extracorporeal treatment of plasma from the subject by affinity adsorption column chromatography, wherein the column comprises a peptide having an amino acid as set forth in SEQ. ID. NO.1, and returning [the] plasma so treated to the subject.

R38 is a peptide sequence isolated from the C-terminal region of mouse laminin  $\alpha$ -chain and has the amino acid sequence:

KEGYKVRLDLNITLEFRTTSK (SEQ ID NO:1)

(Spec. 2:16-23), also referred to as "peptide 5100" (*see id.* at 8:8 and Table 2).

The Examiner rejected claims 8-13 as unpatentable under 35 U.S.C. § 103(a) over Gaubitz<sup>3</sup> in view of Naparstek<sup>4</sup> and Madaio<sup>5</sup> (Ans. 3). According to the Examiner,

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<sup>3</sup> Gaubitz et al., *Prospective Randomized Trial of Two Different Immunoadsorbents in Severe Systemic Lupus Erythematosus*, 11 JOURNAL OF AUTOIMMUNITY 495-501 (1998) ("Gaubitz").

[i]t would have been *prima facie* obvious to ... to perform a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies, as taught by Gaubitz ..., employing the R38 peptide of the '363 patent [Naparstek] ... given the teachings of Madaio ... that dsDNA-Ab from lupus patients also recognize laminin and the '363 patent that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies (*id.* 4).

Appellant argues that none of the references cited by the Examiner show extracorporeal methods of removing antigen-specific antibodies for the treatment of any disease and that his evidence of unexpected results and the failure of others is sufficient to overcome any *prima facie* case of obviousness (Br. 18-19). Appellant relies on four declarations by the inventor,<sup>6</sup> the third of which relies on Graninger<sup>7</sup> and a Gokhale abstract,<sup>8</sup> as well as Hershko,<sup>9</sup> a post-filing date publication coauthored by the inventor.

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<sup>4</sup> US Patent 6,228,363 B1, *Peptides for the Treatment of Systemic Lupus Erythematosus*, issued 8 May 2001 to Yaakov Naparstek, based on Application 09/399,494, filed 20 September 1999 ("Naparstek"). The 069 Application is a continuation-in-part of Application 09/399,494.

<sup>5</sup> Madaio et al., *Emerging Concepts Regarding B Cells and Autoantibodies in Murine Lupus Nephritis: B Cells Have Multiple Roles; All Autoantibodies Are Not Equal*, 7 JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY 387-396 (1996) ("Madaio").

<sup>6</sup> We cite to the Declarations of Yaakov Naparstek dated 19 June 2005 ("Naparstek Decl. I"), 17 September 2007 ("Naparstek Decl. II"), 10 December 2007 ("Naparstek Decl. III"), and 29 June 2008 ("Naparstek Decl. IV").

<sup>7</sup> Graninger et al., *Immunoadsorption Therapy (Therasorb) in Patients with Severe Lupus Erythematosus*, 1 ACTA MEDICA AUSTRIACA 26-29 (2002) ("Graninger").

At issue is whether the preponderance of the evidence supports a *prima facie* conclusion of obviousness; and, if so, whether the proffered evidence of secondary considerations suffices to establish nonobviousness. According to Appellant, claims 8 and 10-13 stand or fall with claim 9. Therefore, we decide this appeal on the basis of claim 9. 37 C.F.R. § 41.37(c)(1)(vii).

## II. Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

### A. Gaubitz

- [1] "Autoantibodies, especially antibodies to double-stranded DNA (dsDNA-Ab), and immune complexes play a pivotal role in the pathogenesis of SLE" (Gaubitz 495, col. 1, ¶ 1).
- [2] Gaubitz developed two immunoabsorption columns to remove pathogenic antibodies and immune complexes in the plasma of SLE patients (*id.* abstract; 498, col. 1, ¶ 2).
- [3] One column, IMPH-350, contained a phenylalanine ligand which binds antibodies via a hydrophobic physicochemical interaction, while the other column, Ig-Therasorb, contained polyclonal sheep antihuman antibodies directed against immunoglobulin  $\kappa$  and  $\lambda$  light chains and IgG heavy chains (*id.* at 497, col. 2, ¶¶ 3-4; Table 1).

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<sup>8</sup> PubMed Abstract 11848331 of Gokhale et al., *Plasmapheresis: an adjunct therapy in severe progressive neuropsychiatric lupus*, 49 J. ASSOC. PHYSICIANS INDIA (2001) ("Gokhale abstract").

<sup>9</sup> Hershko et al., *Removal of Pathogenic Autoantibodies by Immunoabsorption*, 1051 ANNALS NEW YORK ACADEMY OF SCIENCES 635-646 (2005) ("Hershko").

- [4] Extracorporeal plasma separation was performed and the separated plasma was perfused through the immunoadsorption column (*id.* at 497, col. 1, ¶ 2).
  - [5] The IMPH-350 and Ig-Therasorb columns reduced the amount of dsDNA antibodies by  $50.8 \pm 6.6\%$  and  $61.0 \pm 8.0\%$ , respectively, directly after treatment (*id.* abstract).
  - [6] Gaubitz concluded that "immunoadsorption in combination with immunosuppression offers a safe additional option in the treatment of SLE with good, partly long-term efficacy" (*id.* at 500, col. 2, ¶ 3).
- B. Madaio
- [7] Initially, we note that Naparstek teaches that lupus (glomerulo)nephritis is a major cause of morbidity and mortality in SLE (Naparstek 1:20-25).
  - [8] According to Madaio, "[t]he predominant autoantibody-glomerular antigen interaction(s) in a given individual influences the principal location of immune deposition, which in turn influences the pathologic and clinical expression of disease" (Madaio abstract).
  - [9] However, "serum autoantibody levels in patients without clinical evidence of nephritis can be markedly elevated, and, conversely, are occasionally undetectable in patients with fulminant disease" (*id.* at 388, col. 1, ¶ 2).
  - [10] In other words, "not all lupus autoantibodies are pathogenic" (*id.* at 390, col. 2, ¶ 2).
  - [11] Working with inbred strains of mice that spontaneously develop lupus, primarily MRL-*lpr/lpr* mice (*id.* at 388, col. 1, ¶ 3), Madaio observed that nephritogenic autoantibodies cross-reacted with glomerular

basement membrane and cell-surface constituents, including laminin (*id.* at 391, col. 2, ¶ 3).

- [12] Madaio Table 1 shows *in vivo* and *in vitro* properties of selected immune-deposit forming MRL-*lpr/lpr*-derived anti-DNA antibodies reported from a single laboratory and is reproduced below.

TABLE 1. *In vitro* and *in vivo* properties of selected immune-deposit forming MRL-*lpr/lpr*-derived anti-DNA antibodies reported from a single laboratory<sup>a</sup>

| mAb (iso)    | <i>In vitro</i> binding <sup>b</sup> |       |          |         | <i>In vivo</i> <sup>c</sup> |                                  |
|--------------|--------------------------------------|-------|----------|---------|-----------------------------|----------------------------------|
|              | ssDNA                                | dsDNA | anti-RNP | laminin | IF                          | IM                               |
| H147 (IgG2a) | 3+                                   | 2+    | 1+       | 1+      | Linear GBM/TBM mes/cap wall | Proliferative glomerulonephritis |
| H221 (IgG2a) | 3+                                   | 3+    | 2+       | N†      | Intraluminal mes/cap wall   | Intraluminal deposits            |
| H238 (IgM)   | 1+                                   | —     | 2+       | 1+      | Mes/cap wall small vessels  | Hypercellularity                 |
| H151 (IgG3)  | 1+                                   | —     | 3+       | —       | Mes/cap wall small vessels  | Vessel wall thickening           |
| H8 (IgG2a)   | 2+                                   | 2+    | 2+       | —       | Mes/cap wall                | Inconclusive                     |
| H241 (IgG2a) | 3+                                   | 4+    | 2+       | 3+      | Mes/cap wall                | Inconclusive                     |
| H7 (IgG1)    | 1+                                   | 1+    | 1+       | N†      | Intravascular               | Normal <sup>d</sup>              |
| H9 (IgG2a)   | 1+                                   | 1+    | —        | N†      | Intravascular               | Hypercellularity                 |
| H72 (IgG1)   | 1+                                   | 1+    | —        | N†      | Intravascular               | Hypercellularity                 |

<sup>a</sup> IF, immunofluorescence; IM, light microscopy; mes, mesangial; cap wall, capillary wall; N†, not tested; —, nonreactive.

<sup>b</sup> See References, 76–78, 83, and 85 for details of *in vitro* and *in vivo* assessments.

<sup>c</sup> Animals developed proteinuria associated with glomerular epithelial cell foot process effacement.

### C. Naparstek

- [13] Naparstek teaches that peptide R38, a peptide sequence isolated from the C-terminal region of mouse laminin  $\alpha$ -chain and having the amino acid sequence KEGYKVRLDLNITLFTTSK, is recognized by and binds to pathogenic lupus antibodies (Naparstek 1:59-2:1; 3:13-19).
- [14] The amino acid sequence of Naparstek's R38 peptide is identical to the amino acid sequence set forth as SEQ ID NO:1 in claim 9.

### D. The Naparstek Declarations

- [15] Yaakov Naparstek, MD (Naparstek Decls. II and IV, ¶ 1) testified that R38-immunoabsorption removed 86% of the SLE antibodies in an applied sample of mouse monoclonal anti-DNA antibody C72 and 61% of the SLE antibodies in a 1:100 dilution of plasma from an SLE patient (Naparstek Decl. I, ¶¶ 2-3).
- [16] In his second and fourth declarations, Dr. Naparstek testified that the "Luposorb™ immunoabsorption column is an affinity adsorption

column comprising R38 (VRT101) peptide" (Naparstek Decl. II, ¶ 10 and IV, ¶ 8).

[17] Dr. Naparstek further testified that SLE patients scheduled for plasmapheresis will be/were enrolled in a Phase I/II clinical trial on the plasmapheresis day, undergo treatment of between 2-3 hours with the Luposorb™ column, and then be followed up for 8 weeks (*id.*).

[18] In his second declaration, Dr. Naparstek testified that two patients underwent treatment and completed the two-month follow-up period. The attached chart refers to the first patient only. ... As shown in Figure 12, the level of anti-VRT (R38) antibodies decreased after the Luposorb™ apheresis and returned to the original levels after more than 5 weeks (Naparstek Decl. II, ¶ 10).

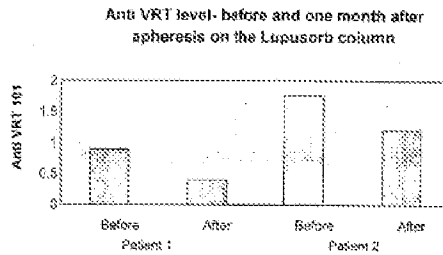
[19] There was no Figure 12 attached to the second Naparstek Declaration.

[20] In his third declaration, Dr. Naparstek stated,

A graph showing antibody levels in two patients pre- and one month post-treatment by methods of the present invention was inadvertently omitted with the last declaration, and it is included herewith. One of the patients did not receive any immunosuppressive treatment, while the other one received only low doses of corticosteroids and azathioprine at the time of treatment with the methods of the present invention. [Naparstek Decl. III, ¶ 3.]

[21] A graph labeled "Figure 1" was attached to the third Naparstek declaration and is reproduced below.

Figure 1



- [22] In his fourth declaration, Dr. Naparstek testified that ten additional SLE patients participated in the Lupusorb™ immunoadsorption clinical trial and that the "[p]atients continued on any drug regimen that had been in place prior to the trial, but no drugs such as cyclophosphamide were administered to combat a potential rebound effect. No rebound effect was observed." (Naparstek Decl. IV, ¶ 8.)
- [23] Dr. Naparstek further testified that in seven patients, "anti-R38 antibodies declined immediately after treatment, and remained low ... four weeks post-treatment" but in 3 patients "anti-R38 antibody levels were not reduced by the treatment" (*id.*).
- [24] According to Dr. Naparstek, prior methods of treating SLE with plasmapheresis removed all immune complexes and antibodies from a patient's blood. Consequently, cyclophosphamide or other immunosuppressive drugs must be administered post plasmapheresis to treat for the ensuing "rebound effect, in which the body compensates for the removal of antibodies by producing an overabundance of antibodies, leading to other deleterious side effects" (Naparstek Decl. III, ¶1).
- [25] Dr. Naparstek relies on Graninger and the Gokhale abstract (*id.*).

- [26] According to the Gokhale abstract, two of three SLE patients treated with plasmapheresis followed by synchronized cyclophosphamide experienced a "[r]ebound flare of disease activity ... between 7<sup>th</sup>-10<sup>th</sup> day requiring additional immunosuppressants or steroids" (Gokhale abstract).
- [27] Graninger reports subjecting SLE patients to Ig-Therasorb immunoglobulin apheresis for periods of 4 to 54 weeks. "In order to prevent rebound autoantibody production, low doses of normal human immunoglobulin were substituted." (Graninger abstract; 27, ¶¶ 2-5).
- [28] According to Graninger, "[t]he concept of removing pathogenic immunoglobulins has thus been further pursued by using advanced technologies that allow removal of the culprit molecules in a more specific manner" (*id.* at 26, last ¶).
- E. Hershko
- [29] Appellant relies on Hershko as "specific support for the proposition that one skilled in the art cannot determine, *a priori*, if methods of treatment using extracorporeal immunoadsorption to remove specific autoantibodies will successfully treat the disease" (Br. 23, original emphasis).
- [30] Hershko was published after the effective filing date of the 069 Application.
- [31] According to Hershko, both nonselective and epitope-specific immunoadsorption methods have been used to remove specific autoantibodies that have been either proved or suspected to play a role in autoimmune diseases (Hershko abstract).

- [32] Known nonspecific immunoadsorption methods, including treatment with phenylalanine (Immunosorba) or sheep anti-human Ig (Ig Therasorb) immunoadsorption columns in conjunction with apheresis systems, are applicable to more than one disease (*id.* at 636, ¶¶ 3-4; 637, Table 1).
- [33] "More recently, attempts have been made to eliminate pathogenic antibodies in an antigen-specific manner with sparing of irrelevant immunoglobulins and other plasma proteins" (Hershko 636, ¶ 1).
- [34] Epitope-specific elimination of autoantibodies "assumes that elimination of these [pathogenic autoantibodies] is sufficient to suppress or reverse the autoimmune process" (*id.* at 638, ¶ 1).
- [35] Hershko tested the validity of this assumption in three model systems: myasthenia gravis ("MG"), dilated cardiomyopathy (DCM), and SLE (*id.*).
- [36] According to Hershko, the MG autoantibodies are mostly directed against the  $\alpha$ -subunit of the acetylcholine receptor (AChR) and either block acetylcholine from binding to AChR (recognize an epitope defined by residues  $\alpha$ 183-200) or enhance AChR degradation and destruction of postsynaptic membrane (recognize epitopes defined by residues  $\alpha$ 67-76 and  $\alpha$ 125-147) (*id.* at 638, ¶ 2).
- [37] Immunization of rats with residues  $\alpha$ 183-200 induces disease, but immunization with residues  $\alpha$ 67-76 does not induce disease unless residues  $\alpha$ 67-76 are linked to a putative T cell stimulatory site defined by residues  $\alpha$ 106-116) (*id.* at 638, last ¶).

- [38] According to Hershko, removing MG antibodies recognizing residues  $\alpha$ 183-200 yielded clinical improvement in one-half to two-thirds of the patients (*id.* at 639, ¶ 2).
- [39] However, according to Hershko, removing MG antibodies recognizing residues  $\alpha$ 67-76 was apparently not feasible due to the low affinity of MG autoantibodies for this epitope (*id.*).
- [40] Hershko concluded that
- patients may benefit from short-term stabilizing therapy by specific removal of pathogenic ... antibodies using plasma perfusion treatment based on the synthetic peptide ( $\alpha$ 183-200)-bound adsorbent. Nevertheless, the specificity of this technique, which is its major advantage, proved to be a significant drawback because the anti-AChR [ $\alpha$ 183-200] blocking antibody is merely one subpopulation among several others implicated in the pathogenesis of MG (*id.* at 639, ¶ 2).
- [41] As to DCM, Hershko stated that "[a] large body of data ... support[s] ... the concept that agonist anti- $\beta$ 1-AR [ $\beta$ 1-adrenergic receptor] IgGs are pathogenic ..." (*id.* at 639, ¶ 5).
- [42] Hershko cited a limited study in which "8 patients were subjected to specific immunoadsorption with peptide columns mimicking the autoantibody-binding epitope of the  $\beta$ 1-AR. Consequently, long-term improvement in cardiac function was detected..." (*id.* at ¶ bridging 639-640).
- [43] As to SLE, Hershko discusses two types of pathogenic anti-dsDNA autoantibodies, i.e., (1) antibodies which bind directly to glomerular structures or form complexes with DNA passively trapped in the glomeruli, and (2) anti-dsDNA antibodies which bind to the laminin

component of the extracellular matrix (*id.* at 640, ¶ 3; 641, ¶ 3; 646 n.53).

[44] As to the latter pathogenic SLE antibody, Hershko states that "[r]igorous analysis of the target epitope disclosed a 21-mer peptide located in the globular part of the  $\alpha$ -chain of laminin" (*id.* at 641, ¶ 3).

[45] According to Hershko, "[p]eptide-bound columns allow specific removal of the pathogenic antibodies, implying that extracorporeal specific immunoadsorption on the laminin-epitope columns may serve as a new therapeutic alternative for SLE" (*id.*).

[46] Hershko concluded that

[t]he nonspecific extracorporeal immunoadsorption may remove all of the putative harmful antibodies, rendering characterization of each individual pathogen redundant. The disadvantage of this approach derives from the unwanted global loss of antibodies against viral and bacterial epitopes as well as protective antibodies that counter-regulate inflammatory processes. These systems may require polyclonal immunoglobulin substitution to reduce the risk of infection and to prevent rebound of autoantibody production. Alternatively, the use of a low-adsorption-capacity system (Prosorba) does not permit substantial removal of immunoglobulins or circulating immune complexes, and its immunomodulatory effects are not yet clearly understood. Specific removal of autoantibodies has the advantage of a potentially high capacity for elimination of the pathogenic agent while sparing immunoglobulins that are irrelevant to the disease process. However, this approach may be hampered by several pitfalls. The identification and isolation of a specific antibody and its target epitope do not guarantee the feasibility of an

efficient column. Such is the case in the modulating antibodies of MG implicated in receptor and membrane destruction, which could not be removed due to low affinity to their corresponding peptide. Furthermore, epitope-specific strategies ignore the possible existence of several pathogenic antibodies in a certain disease, and it is of interest to compare the efficacy and side effects of nonspecific immunoadsorption with specific removal of pathogenic antibodies. [*Id.* at 642, ¶ 2.]

### III. Discussion

#### A. Legal principles

“The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art.” *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In determining whether obviousness is established by combining the teachings of the prior art, “the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). “If a person of ordinary skill in the art can implement a predictable variation, § 103 likely bars its patentability.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

When *prima facie* obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over and Appellant's rebuttal evidence must be evaluated. To that end, “[e]xpected beneficial results are evidence of obviousness of the claimed invention, just as unexpected beneficial results are evidence of unobviousness. *In re Skoll*,

523 F.2d 1392, 1397 (CCPA 1975). Similarly, to show the secondary consideration of failure of others, the evidence must show that others tried and failed to solve the problem. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1980). The failure must be due to the lack of the claimed features. *Ormco Corp. v. Align Technology, Inc.*, 463 F.3d 1299, 1313 (Fed. Cir. 2006).

B. Analysis

The claimed subject matter is directed to a method of treating SLE by selectively removing pathogenic SLE autoantibodies from an SLE subject's blood using immunoadsorption plasmapheresis. Specifically, plasma is removed from the subject and perfused through an immunoadsorption column containing the peptide set forth in SEQ ID NO:1 of claim 9, i.e., peptide R38 (FF 14), which selectively binds to and removes pathogenic SLE autoantibodies therefrom, after which the treated plasma is returned to the subject.

Gaubitz teaches a method of treating SLE in a subject by removing plasma from the subject, perfusing the removed plasma through an immunoadsorption column containing a ligand (phenylalanine or polyclonal sheep antihuman antibody) which nonselectively binds to and removes the antibodies and immune complexes therefrom, after which the treated plasma is returned to the subject (FF 3-4). Gaubitz's nonselective removal of antibodies and immune complexes reduced the amount of anti-dsDNA antibodies by at least half directly after treatment (FF 5). In addition, one of ordinary skill in the art would have reasonably expected that nonpathogenic and/or protective antibodies, such as antibodies against bacterial and viral infection, as well as other plasma proteins would also be lost in a

nonselective immunoadsorption plasmapheresis method (*accord* FF 46). Thus, we agree with the Examiner (*see e.g.*, Ans. 4) that one of ordinary skill in the art would have been motivated to remove pathogenic antibodies in a selective manner in order to avoid removing nonpathogenic and/or protective antibodies and other plasma proteins.

Madaio teaches that pathogenic SLE antibodies cross-react with the glomerular basement membrane and cell-surface constituents, including laminin (FF 8-11). Naparstek teaches that the peptide of SEQ ID NO:1 in claim 9 was isolated from mouse laminin  $\alpha$ -chain and is recognized by pathogenic SLE antibodies (FF 13-14). Thus, we further agree with the Examiner (*see e.g.*, Ans. 4), that it would have been *prima facie* obvious to modify the method of Gaubitz by using an R38 immunoadsorption column to selectively remove the pathogenic SLE antibodies identified by Madaio from a subject's separated plasma and avoid removing nonpathogenic and/or protective antibodies and other plasma proteins. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success based on the laminin-pathogenic SLE antibody binding disclosed by Madaio (FF 11-12) and the specific recognition of an epitope on the laminin  $\alpha$ -chain identified as R38 by pathogenic SLE antibodies as disclosed by Naparstek (FF 13). *Dow Chem. Co.*, 837 F.2d at 473; *Keller*, 642 F.2d at 425.

Appellant's rebuttal evidence of unexpected results (Br. 20-23) and of the failure of others (Br. 20-23) does not persuade us otherwise. We adopt the Examiner's reasoning and add the following for emphasis.

Appellant argues that a skilled artisan cannot determine *a priori* if extracorporeal immunoadsorption to remove specific autoantibodies will successfully treat an autoimmune disease, relying on Hershko's discussion of

MG, DCM, and SLE as model autoimmune diseases (Br. 23). Hershko fairly teaches and/or suggests that treatment of an autoimmune disease by extracorporeal immunoadsorption of antibodies requires not only identifying which subset(s) of autoantibodies are *pathogenic*, but also identifying their cognate *antigen* (target epitope) so that the *pathogenic* autoantibodies can be removed by specifically binding to their cognate *antigen(epitope)* using an epitope-specific immunoadsorption method (FF 33, 46). In other words, Hershko provides one of ordinary skill in the art with a framework reasonably expected to lead to successful treatment of an autoimmune disease.

Autoimmune diseases by definition are diseases that occur when the body's immune system produces antibodies which attack and destroy its own antigens and tissues, i.e., autoantibodies. Not all autoantibodies are pathogenic (*see e.g.*, FF 9-10) and there may be more than one type of autoantibody (*see e.g.*, FF 11-13, 36, 43). In the case of SLE, the pathogenic autoantibodies and their cognate ligands have been identified and shown to specifically bind to each other *in vivo* and *in vitro* (FF 1, 11-13, 43). The failure of others to successfully treat MG, for example, by an epitope-specific  $\alpha$ 183-200 and/or  $\alpha$ 67-76 immunoadsorption method is neither evidence that others tried and failed to successfully treat SLE by an epitope-specific immunoadsorption method, *Stratoflex*, 713 F.2d at 1540, nor evidence that the failure was due to the lack of an epitope-specific SEQ ID NO: 1 (R38) immunoadsorption method. *Ormco Corp.*, 463 F.3d at 1313.

As shown by Hershko, different autoimmune diseases produce their own set of autoantibodies that recognize different antigen(s)/epitope(s) (FF 36, 41, 43). In the case of MG, one subset of autoantibodies was pathogenic

when it specifically bound to epitope  $\alpha$ 183-200 (FF 36, 37, 46), while another subset of autoantibodies was pathogenic only when it bound to epitope  $\alpha$ 67-76 linked to  $\alpha$ 106-116 (FF 37). As pointed out by the Examiner (Ans. 14), removal of MG autoantibodies recognizing residues  $\alpha$ 67-76 was apparently not feasible due to the low affinity of these autoantibodies for  $\alpha$ 67-76 (FF 39). Furthermore, as indicated by Hershko, an epitope-specific  $\alpha$ 183-200 immunoabsorption method specifically removes one subset of MG pathogenic autoantibodies but not several other subsets of MG pathogenic autoantibodies (FF 40). In the case of DCM, Hershko teaches that anti- $\beta$ 1-AR antibodies are pathogenic (FF 42) and that a specific binding epitope  $\beta$ 1-AR immunoabsorption treatment method resulted in long-term improvement (FF 42). Thus, Hershko does not persuade us that others have tried and failed to treat SLE by removing pathogenic autoantibodies using an epitope-specific immunoabsorption method based on MG and DCM epitope-specific immunoabsorption methods.

Appellant also argues that the claimed method produces unexpected results as shown by the Naparstek declarations (Br. 20-23). For example, Dr. Naparstek testified that no rebound effect was observed in SLE patients participating in the Lupusorb<sup>TM</sup> immunoabsorption clinical trial, although no drug such as cyclophosphamide was given (FF 22). However, claim 9 does not preclude administering an immunosuppressive drug and, therefore, this showing is not commensurate in scope with the claimed invention. We also note that one of the patients discussed in the third Naparstek declaration received immunosuppressive drugs "at the time of treatment with the methods of the present invention" (FF 20). Furthermore, the only evidence of a rebound effect pointed to by Appellant is in the context of removing *all*

of the antibodies from a patient's plasma (FF 24-27). Appellant has not pointed to evidence of record showing that one of ordinary skill in the art would have reasonably expected the same rebound effect to occur from selectively removing a single type of antibody. Absent such evidence, Appellant has not shown that his results are unexpected.

Appellant further argues that "as attested to in the Third Declaration, the treatment methods of the invention worked, and further showed an unexpected decline in serum autoantibody levels post-treatment" (Br. 21). However, this conclusory statement by Appellant fails to explain why the decline in serum autoantibody levels post-treatment was unexpected. Even non-selective immunoadsorption methods reduce autoantibody levels post-treatment (*see e.g.*, FF 5). Therefore, this argument is not persuasive.

Finally, Appellant's arguments of unpredictability based on the small size of R38, possible changes in conformation due to attaching to a substrate, possible affinity differences of "R38 antibodies" for R38 versus Ig-Therasorb (sheep polyclonal antihuman antibodies), an undefined "very low level of anti-R38 antibodies in plasma," and "the plasma flow rate required to make this method of treatment viable" (Br. 20) are not persuasive for the reasons set forth by the Examiner (*see e.g.*, Ans. 7-8). We also note that the method of claim 9 does not require any specific plasma flow rate and that Appellant has neither argued nor suggested that determining a suitable plasma flow rate is not a routine matter of optimization well within ordinary skill in the art.

### C. Conclusion

We sustain the rejection of claims 8-13 under 35 U.S.C. § 103(a) over Gaubitz in view of Naparstek and Madaio because the preponderance of the

evidence supports a *prima facie* conclusion of obviousness and the proffered evidence of secondary considerations fails to establish nonobviousness.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner to reject claims 8-13 as unpatentable under 35 U.S.C. § 103(a) over Gaubitz in view of Naparstek and Madaio is AFFIRMED, and

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R.

§ 1.136(a)(12)(vi).

AFFIRMED

alw

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